LAW OFFICES
SUGHRUE, MION, ZINN, MACPEAK & SEAS, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
WASHINGTON, DC 20037-3213
TELEPHONE (202) 293-7060
FACSIMILE (202) 293-7860
www.sughrue.com

December 12, 2000

BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

PCT/GB98/01722
-filed June 12, 1998

Re: Application of Richard H. JONES , Dietrich BRANDENBURG, , Fariba SHOJAEE-MORADI,and Jens KLEINJUNG
INSULIN ANALOGUE
Our Ref: Q62257

Dear Sir:

The following documents and fees are submitted herewith in connection with the above application for the purpose of entering the National stage under 35 U.S.C. § 371 and in accordance with Chapter II of the Patent Cooperation Treaty:

☑ an English translation of the International Application.

☑ International Search Report and PTO Form 1449 listing the ISR references.

☑ a Preliminary Amendment

☑ International Preliminary Examination Report.

The Declaration and Power of Attorney, Assignment, will be submitted at a later date.

It is assumed that copies of the International Application, the International Search Report, the International Preliminary Examination Report, and any Articles 19 and 34 amendments as required by § 371(c) will be supplied directly by the International Bureau, but if further copies are needed, the undersigned can easily provide them upon request.

The Government filing fee is calculated as follows:

Total claims	15	-	20	=	_____	x	$18.00	= $.00
Independent claims	1	-	3	=	_____	x	$80.00	= $.00
Base Fee								$860.00
Multiple Dependent Claim Fee								$270.00
TOTAL FEE								$1130.00

A check for the statutory filing fee of $1130.00 is attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.492 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

There is no claim to priority.

The Office is invited to contact the above firm on any question which might arise on the above-named application. Any contact that the Office might need to make should be directed to Mr. Thomas J. Macpeak , Registration No. 19,292 , at (202)293-7060.

Respectfully submitted,

Waddell A. Biggart
Registration No. 24,861

WAB/plr

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Richard H. JONES , et al.

Appln. No.: Not Yet Assigned — Group Art Unit:

Filed: December 12, 2000 — Examiner:

For: INSULIN ANALOGUE

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 1, line 17, delete "thyroxine binding proteins (TBP)" and insert therefor --thyroid hormone binding proteins (THBP).--.

Page 2, line 35, after "rendered" please insert --or the B1 residue of insulin.--.

Page 2, Line 4, delete "is not a naturally occurring compound. It" and insert therefor -- rT3 is a naturally occurring compound, but is inactive as a thyroid hormone.--

Line 8, delete "thyroxine binding proteins" and insert therefor --thyroid hormone binding proteins--;

line 10 delete "TBP's" and insert therefor --THBP's--.

Page 3, line 23, delete "thyroxine binding proteins," and insert therefor --thyroid hormone binding proteins,--.

Page 4, line 1, 3, 5 and 7, delete "125-Insulin" and insert therefor --125 I-insulin--.

Line 4, delete "rT3" and insert therefor --rT3-Ins--.

Page 4, line 3 delete "TBP" and insert therefor --THBP--;

Line 7 delete "TBP" and insert therefor --THBP;

Line 8 delete "TBP" and insert therefor --THBP.

AMENDMENT
Attorney Docket No. Q62257

IN THE CLAIMS:

Page 10, claim 1, line 2, delete "triiodothyromine", and insert therefor --triiodothyronine--.;

claim 2, line 2, delete "triiodothyromine", and insert therefor --triiodothyronine--;

claim 3, line 1, delete "claim 2" and insert therefor --claim 1--;

line 2, delete ""triiodothyromine", and insert therefor --triiodothyronine--; delete "lysine" and insert therefor --residue.--;

claim 5, line 1, delete "to any preceding claim" and insert therefor --to claim 1--;

claim 6, line 2, delete "to any of claims 1 to 4" and insert therefor --to claim 1--;

claim 7, line 2, delete " to any of claims 1 to 4" and insert therefor --to claim 1--;

Please delete claim 8;

Please delete claim 9;

Please insert the following new claims:

Claim 10. A composition comprising a compound according to claim 3 and a carrier.

Claim 11. A pharamaceutical composition comprising a compound according to claim 3 and a pharmaceutically acceptable carrier.

Claim 12. A method of treatment of a human or other animal by insulin repalcement therapy in which a compound according to claim 1 is administered to the human or other animal.

Claim 13. A method of treatment of a human or other animal by insulin replacement theraphy in which a compound according to claim 3 is administered to the human or other animal.

Claim 14. A method according to claim 12 or claim 13 in which the human or other animal is suffering from diabetes.

Claim 15. A method according to claim 12 or claim 13 in which the compound is administered into the circulation of the said human or animal.

REMARKS

Entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,

Waddell A. Biggart
Registration No. 24,861

SUGHRUE, MION, ZINN,
MACPEAK & SEAS, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

INSULIN ANALOGUE

The present invention relates to novel insulin analogues which are covalent conjugates of an insulin molecule and a derivative of the hormone thyroxine, 3,3',5'triiodothyronine.

In WO-A-95/05187 we described novel insulin conjugates with hormones, specifically with tetraiodothyroxine (3,3',5,5'tetraiodothyronine, T4), which were hepatoselective. The hepatoselectivity was believed to be due to the fact that, when introduced percutaneously, the size of the molecule (about 15% higher molecular weight than insulin itself) allows it to diffuse through the capillary endothelium into the circulation. In the circulation it is believed to bind reversibly the circulating proteins having an affinity for the thyroxine moiety, namely throxine binding globulin, thyroxine binding prealbumin and albumin, collectively known as thyroxine binding proteins (TBP). These higher molecular weight complexes are then unable to diffuse back through capillary endothelium, but are able to diffuse through the relatively larger pores of the hepatic endothelium. The conjugate is found to retain insulin activity. The hepatoselectivity ensures that insulin is directed to the site where its activity is required.

In WO-A-95/07931 hydrophobically modified insulin analogues are described. The insulin is generally derivatised by acylation of the pendant amino group of lysine at B29 with a fatty acid. However there is also an example of derivatising that residue with thyroxine, or with tetraiidothyroacetic acid. The analogues are alleged to have a protracted profile of action, although the mechanism by which this takes place is not elucidated.

One potential problem with the T4-insulin conjugate is that it may retain thyroxine activity. The present invention seeks to solve this problem while providing a conjugate which retains its hepatoselectivity, insulin activity and circulating protein affinity.

A new compound according to the invention comprises an insulin molecule covalently bound to 3,3',5'-triiodothyronine.

The 3,3',5'triiodothyronine molecule is not a naturally occurring compound. It is an isomer of 3,5,3' triiodothyronine (T3) and is consequently known as reverse T3, rT3. It has insignificant activity on thyroxine receptor, but thyroxine binding proteins have an affinity for the molecule. Thus the compound of the invention should have affinity for TBP's and, it is believed, consequential hepatoselectivity whilst the compound and its metabolites should not stimulate thyroxine activity.

The rT3 moiety should be conjugated to a residue of the insulin molecule such that insulin activity is not adversely affected. As in WO-A-95/05187, conjugation is preferably through the B1 residue of insulin. Alternatively the B29 residue may be linked to rT3. In WO-95/07931, the B29 residue may be derivatised and the methods of conjugating a carboxylic acid-containing compound to the B29 residue as disclosed in that reference may be used in the present invention.

The insulin may be made by recombinant DNA techniques or may be isolated from natural sources, human or animal. Recombinant insulin may have deleted residues as desired, for instance the B29 residue may be deleted. Other residues of naturally occurring insulin may be substituted, usually by conservative substitutions. For instance in WO-A-95/07931, analogues in which the B3 and/or A21 residues are other than those of naturally occurring insulin.

The rT3 molecule is conjugated to the insulin using conventional biochemical techniques in which pendant groups on the appropriate residue of the insulin molecule are covalently bonded to rT3, through the carboxylate group. The pendant group is usually the e-amino group of a lysine residue. Any other lysine residues may be rendered unreactive by protecting the e-amine groups using

conventional techniques. Protecting groups are removed after conjugation to the rT3 molecule.

The phenolic OH group of rT3 is protected during the process, also.

Either or both of the amine group and the carboxylate group may be activated prior to contact of the insulin with the rT3. Conventional techniques for generation of amide linkages may be used, for instance using known reagents.

A spacer may be included between the insulin molecule and the rT3 molecule. A spacer may, for instance, improve retention of insulin activity and/or TBP-binding. A spacer may also be used to control *in vivo* cleavage and metabolism of the conjugate compound, and consequently its insulin activity. A spacer may, for instance include a chain comprising 2 to 22 carbon and/or heteroatoms, such as a 4-10 atom chain, preferably comprising an alkylene group and carbonyl and/or amino groups, amido groups and or oxygen atoms in ester or ether linkages.

The inventors have found that the insulin-rT3 conjugate has a similar potency relative to human insulin itself. This is in contrast to T4-insulin, which appears to have a greater potency than human insulin. In the presence of binding proteins, especially thyroxin binding proteins, the potency of T4-insulin is reduced, whereas these proteins do not affect the potency of rT3-insulin. These data indicate that the conjugate is likely to have similar effects as insulin *in vivo*.

Further tests in which the ED50 of the conjugates as compared to insulin, in the presence and absence of binding proteins (human serum albumin and thyroxin binding globulin and transthyretin) show that each conjugate on its own has a similar ED50 to human insulin itself. The ED50's of the T4-insulin conjugate are significantly increased by the presence of TBG, whilst the ED50's of the rT3-insulin are not effected to a significant degree.

We have also conducted competitive binding assays of the insulin analogues compared to human insulin with

^{125}-Insulin to insulin receptors on liver plasma membrane (LPM). Insulin is known to inhibit the binding of ^{125}-Insulin to these receptors. We have found that TBP does not affect this ability. rT3 behaves in a similar way to human insulin in that it inhibits binding of ^{125}-Insulin to the receptors on LPM and this is not affected by the presence of TBP. T4 insulin itself does inhibit ^{125}-Insulin binding to these receptors. In contrast, however, TBP significantly affects this inhibition.

The novel compound is suitable for use in a method of treatment of the human or animal, for instance to replace insulin in a method of insulin replacement therapy. The invention thus comprehends novel compositions containing the compound as well as pharmaceutical compositions containing the compound and a pharmaceutically acceptable excipient. The composition is formulated so as to be suitable for administration by the usual routes, generally by subcutaneous injection. Accordingly the carrier is generally aqueous. The invention comprehends also a new use of the compound in the manufacture of a medicament for use in a method of treatment of the human or animal body.

The following examples illustrate the invention.

Example 1
Preparation of [rT3(Na-B1)]-insulin

1.1 Synthesis of Msc-rT3

50.0 mg rT3 (76.8 umol, 651.0 g/mol)
20.4 mg Msc-OSu (76.9 umol, 265.24 g/mol)

50.0 mg rT3 were suspended in 400 ul dimethylformamide and 20.4 mg Msc-OSu, dissolved in 100 ul dimethylformamide, were added. 4 ul of triethylamine were pipetted into the solution and the mixture was stirred overnight at room temperature.

1.2 Synthesis of Msc-rT3-OSu

16.6 mg DCC (80.6 umol, 206.3 g/mol)

16.6 md DCC were dissolved in 50 ul dimethylformamide and added to the above reaction mixture. The activation is complete after 3 h at room temperature.

1.3 Synthesis of [rT3(Na-B1)]-insulin

230 mg A1,B29-(Msc)2-insulin (6078 g/mol, 38 umol) synthesised according to Schüttler A and Brandenburg D, Hoppe-Seyler's Z. Physiol.Chem. 360, 1721-1725 (1979) were dissolved in 3 ml dimethylformamide with the addition of 4 ul triethylamine and then reacted with 69 ug Msc-rT3-OSu (898 g/mol, 76 umol, two-fold excess with respect to insulin derivative). After stirring for 3 h at room temperature the acylation was stopped by addition of 50 ul acetic acid. The solution was dialysed overnight against distilled water and lyophilised. For cleavage of Msc protecting groups the protein material was diluted in a mixture of 1 ml dimethylformamide, 1.5 ml methanol and 1.5 ml water. The solution was cooled to 0°C and addition of 0.5 ml of ice-cold 2 M sodium hydroxide solution started the cleavage reaction. The reaction was stopped by acidification with 1 ml of 10% (v/v) acetic acid. The protein was precipitated by pipetting the reaction solution into a mixture of 250 ml of ice-cold ether and 20 ml methanol and stirring for 1 h. The ether was decantated from the precipitated protein and the protein dried in vacuo.

Purification of the raw material was performed by use of RP-MPLC. Fractions were collected and lyophilised. Chromatographic conditions:

Column: RP20C18, 2.5 x 250 mm, 122 ml total volume,

Gradient: 25-40% (v/v)

2-propanol in water containing 0.1% trifluoro acetic acid, total gradient volume 1.5 l; flow rate 20 ml / 3 min.

Yield: 27 mg (10% of theory, based on A1,B29-(Msc)2-insulin)

Molecular mass: 6437 u (calc. 6436.6 u)

Purity (RP-HPLC): 93 % (Absorption at 215 nm)

1.4 Mass spectrometry

MS-TOF spectrometer VG TofSpec, Fisons

Ionisation: Ar-laser, MCP Volts,: 1750, 337 nm, linear modus Acceleration: 20 kV

Standard: bovine insulin 5731 u (calc. 5731 u), vasointestinal peptide 1424 u (calc. 1426 u) [rT3(Na-B1)]-insulin: 6437 (calc. 6437)

Example 2 - Effects of Binding Proteins on Receptor Binding

The rT3-insulin conjugate made in Example 1 is used in various tests to determine the binding potencies of the analogues on liver plasma membrane. ^{125}-Insulin is used as the labelled insulin. It is known that insulin itself inhibits binding of ^{125}-Insulin.

Results

Equilibrium binding curves

The equilibrium binding curves of average normalised bound against the log-concentration of insulin or analogue (nmol/l) with or without the presence of THBP were generated. The trends initially illustrated by the curves were:

H-Ins, rT3-Ins and T4-Ins appear similar in their positions, i.e. there is no difference between them in their ability to inhibit the binding of ^{125}-Insulin to insulin receptors on LPM.

The presence of THBP does not appear to affect the ability of H-Ins to inhibit the binding of ^{125}-Insulin to insulin receptors on LPM.

The presence of THBP does not appear to affect the ability of rT3-Ins to inhibit the binding of ^{125}-Insulin to insulin receptors on LPM.

The presence of THBP does appear to affect the ability of T4-Ins to inhibit the binding of ^{125}-Insulin to insulin receptors on LPM as shown by the shift in the T4-Ins+THBP curves to the right. TBG seems to have the greatest effect on T4-Ins, i.e. causes the greatest shift.

ED50

The ED50's as calculated by the G-PIP software were inverse logged because the concentrations entered in G-PIP had to be entered as the log of the concentrations. The average (nmol/1)± SEM of the ED50's was then calculated. The results are shown in Table 1. These give a quantitative idea of the shift, if any in the equilibrium binding curves.

TABLE 1

Average of ED50 ± SEM			
	Average	**SEM**	**n=**
H-Ins	1.966	0.43	5
rT3-Ins	2.455	0.35	6
0.5% HSA	2.48	0.478	4
1% HSA	3.24	0.379	3
2.5% HSA	2.76		2
Transthyretin	1.805	0.55	4
0.135μmol/l TBG	3.147	0.35	3
T4-Ins	1.316	.034	5
0.5% HSA*	3.715		2
1% HSA*	5.823	2.108	3
2.5% HSA*	4.81		2
Transthyretin*	2.935	0.32	4
0.135μmol/l TBG*	21.67	2.258	3
0.27μmol/l TBG*	36.55		2

* Fisher's test also performed.

Statistical analysis of the ED50's

From the statistical analysis it was found that the ED50's of rT3-Ins and T4-Ins were not significantly different from that of H-Ins. The ED50's of rT3-Ins with THBP were not significantly different from those of rT3-Ins without THBP present as determined by ANOVA. On the other hand, the ED50's of T4-Ins without THBP present ($p<0.05$) as determined by Fisher's least squares test (see Table 1*).

Potency estimates

The potency estimates of the analogues relative to H-Ins and the analogues in the presence of THBP relative to the analogues in the absence of THBP are shown in Table 2 with their fiducial limits. This demonstrates that rT3-Ins has a similar potency relative to H-Ins. T4-Ins seems to have a greater potency relative to H-Ins. The presence of THBP seems to have no effect on the binding potency estimates of rT3-Ins binding to insulin receptors relative to rT3-Ins without THBP present. However the presence of THBP present. However the presence of THBP greatly reduces the T4-Ins binding potency estimates relative to T4-Ins binding to insulin receptors without THBP present (Table 2).

TABLE 2

Potency Estimates		
	Potency	95% fiducial limits
H-Ins	100%	
rT3-Ins	94%	56-157
T4-Ins	184%	111-318
rT3-Ins	100%	
0.5% HSA	122%	87-173
1% HSA	87%	58-129
2.5% HSA	119%	80-178
0.135μmol/l TBG	76%	54-107
Transthyretin	183%	111-306
T4-Ins	100%	
0.5% HSA	27%	15-46
1% HSA	31%	16-54
2.5% HSA	35%	19-60
0.135μmol/l TBG	5%	2-9
Transthyretin	33%	20-54

Scatchard Plots

The Scatchard plot of H-Ins demonstrates the characteristic curvilinear shape of negative co-operativity that should be exhibited by human insulin. It may be seen from the Scatchard plots of rT3-Ins and T4-Ins that these analogues also exhibit negative co-operativity due to their curvilinear shape.

Reference Example - Synthesis of Insulin - T4

The T4 insulin is B1-thyroxyl-insulin made according to the technique described in WO-A-95/05187, Example 1.

CLAIMS

1. A compound consisting of an insulin molecule covalently bound to 3,3',5' triiodothyromine.

2. A compound according to claim 1 in which the 3,3',5' triiodothromine is bound to a lysine residue of the insulin molecule.

3. A compound according to claim 2 in which the 3,3',5' triiodothyromine is bound to the B1 lysine residue.

4. A compound according to any preceding claim in which the insulin is human insulin.

5. A compound according to any preceding claim for use in a method of treatment of the human or animal body.

6. A composition comprising a compound according to any of claims 1 to 4 and a carrier.

7. A pharmaceutical composition comprising a compound according to any of claims 1 to 4 and a pharmaceutically acceptable excipient.

8. Use of a compound according to any of claims 1 to 4 in the manufacture of a composition for use in a method of treatment of the human or animal body.

9. Use according to claim 8 in which the method is insulin replacement therapy, preferably for treatment of diabetes.

USA

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled

INSULIN ANALOGUE

the specification of which ☐ is attached hereto or

☐ was filed on 12 JUN 1998 as United States Application Number or PCT International Application Number PCT/GB98/01722 and was amended on (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor`s certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: John H. Mion, Reg. No. 18,879; Thomas J. Macpeak, Reg. No. 19,292; Robert J. Seas, Jr., Reg. No. 21,092; Darryl Mexic, Reg. No. 23,063; Robert V. Sloan, Reg. No. 22,775; Peter D. Olexy, Reg. No. 24,513; J. Frank Osha, Reg. No. 24,625; Waddell A. Biggart, Reg. No. 24,861; Louis Gubinsky, Reg. No. 24,835; Neil B. Siegel, Reg. No. 25,200; David J. Cushing, Reg. No. 28,703; John R. Inge, Reg. No. 26,916; Joseph J. Ruch, Jr., Reg. No. 26,577; Sheldon I. Landsman, Reg. No. 25,430; Richard C. Turner, Reg. No. 29,710; Howard L. Bernstein, Reg. No. 25,665; Alan J. Kasper, Reg. No. 25,426; Kenneth J. Burchfiel, Reg. No. 31,333; Gordon Kit, Reg. No. 30,764; Susan J. Mack, Reg. No. 30,951; Frank L. Bernstein, Reg. No. 31,484; Mark Boland, Reg. No. 32,197; William H. Mandir, Reg. No. 32,156; Brian W. Hannon, Reg. No. 32,778; Abraham J. Rosner, Reg. No. 33,276; Bruce E. Kramer, Reg. No. 33,725; Paul F. Neils, Reg. No. 33,102; Brett S. Sylvester, Reg. No. 32,765; Robert M. Masters, Reg. No. 35,603 and George F. Lehnigk, Reg. No. 36,359.

Direct all correspondence to:

Sughrue, Mion, Zinn, Macpeak & Seas, PLLC,
2100 Pennsylvania Avenue, N.W.,
Washington D.C. 20037-3202
USA

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

Full name of sole or First Inventor: Richard Henry JONES

Inventor's signature: _____

Residence address: London, United Kingdom

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature: _____

Full name of Second Inventor: Dietrich BRANDENBURG

Inventor's signature: Dietrich Brandenburg

Residence address: Reichelsheim, Germany

Post Office address: Sudetenstrasse 63, D-64385 Reichelsheim, Germany

Country of Citizenship: Germany Date of signature: April 6, 2001

Full name of Third Inventor: Fariba SHOJAEE-MORADI

Inventor's signature: _____

Residence address: London, United Kingdom

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature: _____

Full name of Fourth Inventor: Jens KLEINJUNG

Inventor's signature: Jens Kleinjung

Residence address: London, United Kingdom

Post Office address: 2B Tagore House, 6A Glenloch Road, Belsize Park, London, NW3 4BU, United Kingdom

Country of Citizenship: United Kingdom

Date of signature: 13.01.01

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled

INSULIN ANALOGUE

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Direct all correspondence to:
Sughrue, Mion, Zinn, Macpeak & Seas, PLLC,
2100 Pennsylvania Avenue, N.W.,
Washington D.C. 20037-3202
USA

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

Full name of sole or First Inventor: Richard Henry JONES

Inventor's signature: _____

Residence address: London, United Kingdom

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature _____

Full name of Second Inventor: Dietrich BRANDENBURG

Inventor's signature: _____

Residence address: Reichelsheim, Germany

Post Office address: Sudetenstrasse 63, D-64385 Reichelsheim, Germany

Country of Citizenship: Germany Date of signature _____

Full name of Third Inventor: Fariba SHOJAEE-MORADI

Inventor's signature: _____

Residence address: London, United Kingdom

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature _____

Full name of Fourth Inventor: Jens KLEINJUNG

Inventor's signature: _____

Residence address: London, United Kingdom

Post Office address: 2B Tagore House, 6A Glenloch Road, Belsize Park, London, NW3 4BU, United Kingdom

Country of Citizenship: United Kingdom

Date of signature: _____

USA

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on an invention entitled
INSULIN ANALOGUE

the specification of which ☐ is attached hereto or

☐ was filed on 12 JUN 1998 as United States Application Number or PCT International Application Number PCT/GB98/01722 and was amended on (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for a patent or inventor`s certificate, or PCT international application having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date	Priority Not Claimed	Certified Copy Attached? YES	NO
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: John H. Mion, Reg. No. 18,879; Thomas J. Macpeak, Reg. No. 19,292; Robert J. Seas, Jr., Reg. No. 21,092; Darryl Mexic, Reg. No. 23,063; Robert V. Sloan, Reg. No. 22,775; Peter D. Olexy, Reg. No. 24,513; J. Frank Osha, Reg. No. 24,625; Waddell A. Biggart, Reg. No. 24,861; Louis Gubinsky, Reg. No. 24,835; Neil B. Siegel, Reg. No. 25,200; David J. Cushing, Reg. No. 28,703; John R. Inge, Reg. No. 26,916; Joseph J. Ruch, Jr., Reg. No. 26,577; Sheldon I. Landsman, Reg. No. 25,430; Richard C. Turner, Reg. No. 29,710; Howard L. Bernstein, Reg. No. 25,665; Alan J. Kasper, Reg. No. 25,426; Kenneth J. Burchfiel, Reg. No. 31,333; Gordon Kit, Reg. No. 30,764; Susan J. Mack, Reg. No. 30,951; Frank L. Bernstein, Reg. No. 31,484; Mark Boland, Reg. No. 32,197; William H. Mandir, Reg. No. 32,156; Brian W. Hannon, Reg. No. 32,778; Abraham J. Rosner, Reg. No. 33,276; Bruce E. Kramer, Reg. No. 33,725; Paul F. Neils, Reg. No. 33,102; Brett S. Sylvester, Reg. No. 32,765; Robert M. Masters, Reg. No. 35,603 and George F. Lehnigk, Reg. No. 36,359.

Direct all correspondence to:
Sughrue, Mion, Zinn, ~~Macpeak & Seas~~, PLLC,
2100 Pennsylvania ~~Avenue~~, N.W.,
Washington D.C. 20037-3202
USA

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C 1001 and that such willful false statements may jeopardise the validity of the application or any patent issued thereon.

Full name of sole or First Inventor: Richard Henry JONES

Inventor's signature: 

Residence address: London, United Kingdom GBX

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature: 2nd Jan 2001

Full name of Second Inventor: Dietrich BRANDENBURG

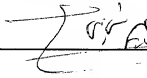
Inventor's signature: _____

Residence address: Reichelsheim, Germany DEX

Post Office address: Sudetenstrasse 63, D-64385 Reichelsheim, Germany

Country of Citizenship: Germany Date of signature: _____

Full name of Third Inventor: Fariba SHOJAEE-MORADI

Inventor's signature: 

Residence address: London, United Kingdom GBX

Post Office address: c/o St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH, United Kingdom

Country of Citizenship: United Kingdom Date of signature: 2/1/2001

400 Full name of Fourth Inventor: Jens KLEINJUNG

Inventor's signature ______________________

Residence address: London, United Kingdom GBX

Post Office address: 2B Tagore House, 6A Glenloch Road, Belsize Park, London, NW3 4BU, United Kingdom

Country of Citizenship: United Kingdom

Date of signature ______________________